PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PS0336-PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/003864	International filing date *(day/month/year)* 13.04.2004	Priority date *(day/month/year)* 14.04.2003
International Patent Classification (IPC) or national classification and IPC G01R33/46		
Applicant AMERSHAM HEALTH R&D AB et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand 17.01.2005	Date of completion of this report 10.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Streif, J Telephone No. +49 89 2399-8194

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003864

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-23 as originally filed

Claims, Numbers

1-15 as originally filed

Drawings, Sheets

1/4-4/4 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/003864

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2,4,6,10-15
	No:	Claims	1,3,5,7-9
Inventive step (IS)	Yes:	Claims	14,15
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The following documents are referred to in this written opinion, the numbering will be adhered to in the rest of the procedure:

D1: US 2002/0006382
D2: Bajaj VS et al, J. Magn. Reson. Vol. 160, pp 85-90 (2003)
D3: Wind RA et al, Advances in chemistry series, American chemical society, Vol. 229, pp 45-63 (1993)
D4: Lyon CE et al, J. Am. Chem. Soc. Vol. 121, pp 6505-6506 (1999)
D5: Zhao L et al, Proc. Int. Soc. Magn. Reson. Med. p. 451 (1998)
D6: Zhao L et al, J. Magn. Reson. B, Vol. 113, pp 179-183 (1996)

1 Re Item V: Reasoned statement under Rule 43bis.1(a)(i) PCT

With respect to the objection under Art. 6 PCT given below (see item 3.1 below), lines 6-11 of claim 1 were replaced by the following clarified features to compare the defined subject-matter with the prior art:

- performing NMR spectroscopy on the sample with the use of sequences of rf pulses, wherein the pulse sequences **comprise** at least two rf pulses, either on the same nuclei or on different nuclei, and wherein **both** pulse sequences is adapted for a hyperpolarized sample, thereby producing at least two **one-dimensional** NMR spectra **or at least one multidimensional NMR spectrum.**

- analysing at least two of the NMR spectra **or the at least one multidimensional NMR spectrum** in order to obtain a characterisation of the sample, or to obtain an interim result to be used in the NMR spectroscopy step.

The search was also based on this clarification.

Accordingly, claim 3 is clarified in that "the pulse sequences **are** adapted ... by using repeated excitation pulses with small flip angles ...".

1.1 Lack of novelty and/or an inventive step (Art. 33(2) and 33(3) PCT)

Claim 1

The subject-matter of claim 1 would appear to lack novelty with respect to each of the documents D1-D4 for the following reasons.

For instance, document D1 discloses (references in parentheses referring to D1):

A method of performing nuclear magnetic resonance spectroscopy on a hyperpolarized sample (see par. [0002], which method comprises the steps of:

- hyperpolarizing a sample using DNP, wherein the NMR active nuclei receive hyperpolarization (D1 implicitly discloses an embodiment wherein hyperpolarization of ^{129}Xe is performed using DNP, see par. [0080]; moreover, ^{129}Xe represents the "NMR active nuclei", see for instance figures 10A-10P and par. [0178]);

- performing NMR spectroscopy on the sample with the use of sequences of rf pulses (see par. [0178] and figures 10A-10P), wherein the pulse sequences comprise at least two rf pulses, either on the same nuclei or on different nuclei (each of the pulse sequences comprises one 20 degree excitation pulse applied to ^{129}Xe, see par. [0178]; furthermore, since a plurality of pulse sequences is applied consecutively (see the time series depicted in figures 10A-10P), it is considered that the pulse sequences comprise at least 2 rf pulses), and wherein the pulse sequence is adapted for a hyperpolarized sample (the use of excitation pulses with a flip angle of 20 degrees (see par. [0178]) is considered to be "adapted for a hyperpolarized sample", see also par. [0174]), thereby producing several two one-dimensional NMR spectra (the plurality of NMR spectra depicted in figures 10A-10P);

- analysing at least two of the NMR spectra in order to obtain a characterization of the sample, or to obtain an interim result to be used in the NMR spectroscopy step (from the plurality of NMR spectra depicted in figures 10A-10P the sample is characterized in that it is concluded that the hyperpolarized "gas remained

substantially in the gas phase", see par. [0178]).

In a similar way, the lack of novelty can be shown with respect to documents D2-D4 (see the passages of these documents cited in the search report).

1.2 Claims 2-13

Claim 2

The subject-matter of claim 2 differs from that of claim 1 only in that an initial 90° pulse followed by a plurality of spin echo pulses is applied rather than a small flip angle pulse as in D1. The corresponding technical effect is an increased signal-to-noise ratio (SNR) of the measurement since the inital 90° pulse generates a higher transverse magnetization than a small flip angle pulse. However, it would appear that the skilled person, desiring to increase the SNR of the measurement, would consider document D5 since the same problem is mentioned therein (see D5, section "Introduction", lines 13-15). The problem is solved in D5 by using a single scan pulse sequence in which one initial 90° pulse is followed by a plurality of spin echo pulses (see section "Introduction", lines 20-29 and section "Methods"). Therefore, it appears that the skilled person would arrive at the subject-matter of claim 2 without the exercise of any inventive skill.

Claims 3, 5

The additional features of claims 3 and 5 are known from D1 as well (see par. [0178]).

Claims 4, 6

The subject-matter of claim 4 differs from D1 in that the flip angle of the excitation pulse is varied rather than kept constant as in D1. However, the advantages of varying the flip angle in the context of an MR experiment involving a hyperpolarized sample are well-known in the art (see e.g. D6). Therefore, it is considered that the skilled person, desiring to provide a constant transverse magnetization throughout the MR experiment, would vary the flip angle of the excitation pulse according to document D6 and arrive at the subject-matter of claim 4 without the exercise of any

inventive skill.

Furthermore, the additional features of claim 6 are known from document D6 as well (see section "Simulation", 1st paragraph; it is noted that the statement that the "flip angle sequence ... uses all the available magnetization" implies that the last excitation pulse is a 90° pulse). Therefore, the subject-matter of claim 6 lacks an inventive step with respect to a combination of documents D1 and D6 as well.

Claims 7-9

The additional features of claims 7-9 are disclosed in each of the documents D2 and D4 (see for instance D2, figures 4 and 5; w.r.t. claim 8 it is noted that the experiment disclosed in D2 can be considered to explore the multidimensional time space "through a trajectory that spans all parts ... that provide essential information"; w.r.t. claim 9 see the two-dimensional experiment disclosed in figure 4 of D2).

Claim 10

Claim 10 would appear to define a simplified version of a heteronuclear COSY experiment wherein two one-dimensional spectra rather than one two-dimensional spectrum are acquired. However, a two-dimensional **homo**nuclear COSY experiment is disclosed in document D2 (see e.g. figure 4). Furthermore, the possibility of performing **hetero**nuclear COSY experiments to correlate the chemical shifts of different kinds of nuclei in order to determine which nuclei are directly bonded to one another is well-known in the art and even D2 itself hints at the possibility of performing "multidimensional correlation experiments" (D2, page 89, last paragraph).

Moreover, the simplification of acquiring two one-dimensional spectra rather than one two-dimensional spectrum cannot be considered to involve any inventive skill since it is well-known in the art that all information that is present in two one-dimensional spectra (and even more) is also accessible via a corresponding two-dimensional spectrum. Therefore, it is considered that the subject-matter of claim 10 lacks an inventive step with respect to document D2.

Claims 11, 12

Claims 11 and 12 specify that the spectroscopy step comprises decoupling of the first and second nuclei. However, spin decoupling in order to simplify NMR spectra by removing the splittings caused by scalar coupling among the decoupled nuclei is well-known in the art (documents will be cited if necessary). Therefore, it would appear that the subject-matter of claims 11 and 12 does not involve any inventive step with respect to document D2 as well.

Claim 13

Claim 13 specifies that the pulse sequence of the NMR spectroscopy method is diffusion weighted. However, this possibility, its implementation using bipolar magnetic field gradients and its advantages are well-known in the art (documents will be cited if necessary). Therefore, it is considered that the skilled person, for instance starting from D2 and desiring to characterize the interaction between proteins and ligands, would add diffusion weighting to the NMR experiment disclosed in D2 and arrive at the subject-matter of claim 13 without the exercise of any inventive skill.

Novelty and inventive step of claims 14, 15

Claims 14 and 15 specify particular trajectories through a multidimensional time-space in the context of a multidimensional NMR spectroscopy method on a hyperpolarized sample. None of the prior art documents cited in the search report addresses the problem of selecting a particular trajectory at all. Therefore, it would appear that the skilled person finds no indication in the prior art to perform a multidimensional NMR spectroscopy experiment that involves the particular trajectories defined in claims 14 and 15, respectively. Thus, the subject-matter of claims 14 and 15 is considered to be novel and inventive.

2 Re Item VIII: Lack of clarity and support in the description

2.1 Claim 1

a) The wording "pulse sequences comprises at least two rf pulses" is obscure. However, with respect to the embodiment disclosed on pages 9-11 of the description wherein two one-dimensional spectra of 1H and 13C are recorded, respectively, it would appear that **each** pulse sequence comprises **only one** rf pulse.

b) The wording "thereby producing at least two NMR spectra" would appear to represent a contradiction to the embodiments given on pages 14-18 of the description wherein only **one** two-dimensional spectrum is produced.

c) It is not apparent what is to be understood by the term "an **interim result** to be used in the NMR spectroscopy step".

d) Moreover, the wording recited in item d) is obscure since the "spectroscopy step" has already been finished when the "interim result" is obtained. Therefore, it is unclear how the "interim result" can "be used in the NMR spectroscopy step".

2.2 Claim 2

It is unclear whether "spin echo pulses" correspond to inversion pulses that flip the magnetization by an angle of 180°.

2.3 Claim 3

The scope of the relative term "**small** flip angles" is unclear. The same objection applies to claim 12 as well.

2.4 Claim 4

The broad scope of the wording "flip angle ... is varied" appears not to be supported by the description. The description merely supports that the flip angle is varied such that an equal amount of transverse magnetization is produced throughout the series of "repeated excitation pulses with small flip angles" (see the description, page 13,

lines 19-24). Therefore, the features of claim 6 should have been added to claim 4.

2.5 Claim 5

The scope of the wording "**essentially** constant" is unclear. Therefore, the word "essentially" should have been deleted.

2.6 Claim 7

a) There appears to be a contradiction between claim 7 (defining a multidimensional NMR spectroscopy experiment) and claim 1 (defining that "at least two NMR spectra" are produced) since a multidimensional NMR spectroscopy experiment normally provides only one multidimensional NMR spectrum.

b) It is unclear whether the term "pulses" in line 28 refers to rf pulses, gradient pulses, etc.

c) The term "the time parameters" lacks an antecedent definition.

d) It is unclear whether the feature defining that "said pulse sequence being adapted to take into account the initial hyperpolarized spin state" corresponds to the specification in claim 1-3 defining that "the pulse sequence is adapted for a hyperpolarized sample".

2.7 Claim 8

It is not apparent what is to be understood by the term "essential information". Therefore, claim 8 is obscure.

2.8 Claim 9

It is not apparent what is to be understood by the term "two time plane". It would appear that this term corresponds to the "multidimensional time space" defined in claim 7.

2.9 Claim 10

The wording "identifying in the first spectr**a**" is obscure since only one "first ...

spectrum" is recorded.

2.10 Claims 14, 15

It is not apparent what is to be understood by the point coordinates (e.g. "point (0,0)", "points (i,i)", "points (N,N)") since the underlying space has not been defined.

2.11 Description and drawings

a) The statements throughout the description according to which certain documents are "incorporated by reference" should have been deleted.

b) The labeling of figures 2a and 2b appears to be incorrect (see page 12 of the description).

c) The speculative broadening by referring to a "future method of hyperpolarization" on page 6, line 24 should have been deleted.